SAGE reference

The SAGE Encyclopedia of Abnormal and Clinical Psychology

Bipolar Disorders: Biological Factors

Bipolar disorders are a group of disorders characterized by the experience of alternative depressive and manic episodes. Manic episodes refer to periods of time during which the individual experiences extreme elevated, irritable, or expansive moods. Bipolar disorders are on a spectrum including bipolar I disorder (characterized by full-blown manic episodes), bipolar II disorder (characterized by depression and less severe hypomanic episodes), and cyclothymia (characterized by cycling periods of hypomania and depression that do not meet full criteria for either hypomania or depression). Numerous biological factors are associated with the development and maintenance of bipolar disorders including neurochemical factors, genetic factors, and brain structure and function.

In this entry, the key neurotransmitters implicated in bipolar disorders are reviewed, including norepinephrine, dopamine, serotonin, glutamate, gamma-aminobutyric acid (GABA), and acetylcholine. Next, neuroendocrine systems including the hypothalamic-pituitary-thyroid (HPT) axis and the hypothalamic-pituitary-adrenal axis are reviewed. Then, genetic factors comprising both behavioral and molecular genetic findings are reviewed. Finally, findings from structural and functional brain imaging studies are reviewed that have suggested structural abnormalities in the prefrontal-striatal-thalamic loop and alternating patterns of functional abnormalities related to whether the individual is currently experiencing a manic or a depressive episode.

Neurochemical Factors

Neurotransmitter Systems

One theory of bipolar disorder is that it is related to a dysregulation of a group of neurotransmitters called monoamines, which include norepinephrine, dopamine, and serotonin. In addition, three other neurotransmitters—(1) glutamate, (2) GABA, and (3) acetylcholine—are thought to play a role in bipolar disorder.

Norepinephrine is a neurotransmitter that is involved in a general response to stress. In bipolar disorder, it is associated with the experience of mania. The main pharmacological treatments for bipolar disorder, including lithium, valproate, and carbamazepine, all work by influencing norepinephrine and/or its downstream targets. The actions of lithium are important in understanding bipolar disorder because research suggests that it is effective in the treatment of bipolar disorder but not in the treatment of other disorders that share similar symptoms. Thus, the finding that lithium influences norepinephrine suggests that norepinephrine regulation is important in bipolar disorder.

The second monoamine implicated in bipolar disorder, dopamine, has different effects in different areas of the brain. In the midbrain, dopamine is linked to reward, motivation, and motor activity. In subcortical structures that are part of the mesolimbic system, dopamine is associated with reward processing, motivational salience, and goal-directed activity. Research suggests that dopamine dysregulation may be important when individuals switch from a manic to a depressive episode, or vice versa. In contrast, the role of serotonin in bipolar disorder is not as well established, but some research suggests that it is related to bipolar disorder.

In addition to monoamines, GABA, acetylcholine, and glutamate have been hypothesized to be involved in bipolar disorder. GABA decreases the activity of its target neurons and is the main inhibitory neurotransmitter in the central nervous system. In individuals with bipolar

disorder, abnormalities in GABAergic neurons have been found in the hippocampus, striatum, anterior cingulate cortex, and hypothalamus. Lithium and valproate may also influence GABA activity.

Like GABA, acetylcholine is also affected by lithium. Lithium increases the synthesis, transport, and release of acetylcholine in the brain. The cholinergic-aminergic balance hypothesis postulates that depression is related to a higher cholinergic activity (i.e., the system by which acetylcholine functions) and a lower aminergic activity (i.e., the system by which monoamines function). Higher aminergic compared with cholinergic activity is related to manic episodes, which further clarifies the role of both acetylcholine and monoamines in bipolar disorder.

Glutamate is the primary excitatory neurotransmitter in the central nervous system. In bipolar disorder, researchers have found a decreased density of glutaminergic cells in several areas of the brain, including the anterior cingulate cortex and the hippocampus. In individuals with either depression or bipolar disorder, a similar decreased density was found in the dorsal lateral prefrontal cortex.

Neuroendocrine Systems

The endocrine system is the mechanism by which hormones enter into the nervous system and affect the brain and the body. The most strongly implicated endocrine pathway in bipolar disorder is the HPT axis. Evidence for the role of the HPT in bipolar disorder comes from the observation that disorders of the HPT axis are often associated with mood changes. In addition, thyroid medication has shown some effectiveness in treating rapid cycling bipolar disorder. The hypothalamic-pituitary-adrenal axis is also likely involved in bipolar disorder, based on observations of increased plasma cortisol levels in patients with bipolar disorder who are in a depressed mood state.

Genetic Factors

Genetics plays a significant role in the pathogenesis of bipolar disorder, with heritability estimates as high as 80% to 90%. Bipolar disorder shows genetic overlap with other mental health disorders, most notably schizophrenia and major depressive disorder. Evidence strongly suggests polygenetic contribution to bipolar disorder risk, meaning that it is likely that there are many risk alleles, each contributing a relatively small amount of risk, that combine to form a diathesis for bipolar disorder.

Although no genes have reached universal acceptance as risk genes for bipolar disorder, linkage studies and genome-wide association studies have identified several candidate risk genes. Promising candidate genes include *BDNF*, *DAOA*, *DISC1*, *TPH2*, and *SLC6A4*. Additional genes implicated by genome-wide association studies include *DGKH*, *CACNA1C*, and *ANK3*. These candidate genes are implicated in a variety of processes, including synaptic function, neural plasticity, cell apoptosis, and cell differentiation during development.

For example, *BDNF* plays an important role in neuronal and synaptic growth and maintenance. Serum levels of the *BDNF* protein, for which the gene codes, have been associated with affective, cognitive, and motor symptoms in several mental health disorders. Lithium and valproate both increase serum levels of the *BDNF* protein. *DAOA*, however, encodes proteins that take part in glutaminergic signaling. *CACNA1C* has received

particularly strong support in genome-wide association studies. This gene codes for a specific calcium channel subunit and, thus, may be involved in observed calcium level abnormalities in bipolar disorder.

Genes involved in circadian functioning, such as *ARNT*-like protein 1, *TIMELESS*, and *PERIOD3*, have also been linked to bipolar disorder. These genes may contribute to observed disturbances in sleep, activity, hormones, and appetite in bipolar disorder. Many genes linked to bipolar disorder risk also encode mitochondrial proteins. Mitochondrial function has been found consistently aberrant in bipolar disorder and affects synaptic function and plasticity, apoptosis, genetic transcription, and calcium levels within cells. The level of calcium may in turn affect neurotransmitter function.

Brain Structure and Functioning in Bipolar Disorder

Neuroscientists use several different tools in studying brain structure and function. The structure of the brain refers to the sizes of brain structures, and researchers typically attempt to find differences between people with bipolar disorder and people without a mental health disorder (i.e., healthy controls) or people with a different mental health disorder (i.e., psychiatric controls). The two most common tools to study brain structure are (1) structural magnetic resonance imaging and (2) computerized tomography.

Brain Structure

One pathway implicated in the pathogenesis of bipolar disorder is the prefrontal-striatal-thalamic loop, which is important in modulating human behaviors, emotions, cognitions, and social behaviors. Some research suggests that the prefrontal cortex is smaller in people with bipolar disorder compared with healthy controls. In particular, people with bipolar disorder may have less gray and white matter in the left superior, right, and middle prefrontal subregions, and the longer an individual has had bipolar disorder, the larger these differences are in volume. The prefrontal cortex is responsible for executive functioning, planning, complex thought, and problem solving.

The next structure in this pathway is a subcortical structure called the striatum. As mentioned, bipolar disorder is thought to be associated with increased dopamine activity, which is related to reward processing and may explain the excessive goal-directed behavior common in mania. The main area of the brain in which rewards are processed is the striatum. Unsurprisingly, people with bipolar disorder have been shown to have increased striatum volume compared with healthy controls. Similarly, the thalamus, the final structure in this loop, has also been shown to have increased volume in people with bipolar disorder.

Other works suggest that medial temporal structures have decreased volumes in people with bipolar disorder. For example, the anterior cingulate cortex has been shown to be smaller in people with bipolar disorder compared with healthy controls. The anterior cingulate cortex is responsible for error recognition, conflict monitoring, and reward-based learning. The amygdala, a brain region associated with emotion processing, in general, and fear, in particular, has been found to be smaller in adolescents with bipolar disorder but may actually be larger in adults with bipolar disorder compared with healthy controls. It is possible that this change is related to lithium treatment, which has been shown to increase amygdala volumes. The hippocampus, a region associated with memory, has been shown to have a similar pattern. Finally, the midline cerebellum has been found to have a decreased volume in people with bipolar disorder.

Brain Function

Along the lines of structural brain differences, people with bipolar disorder have demonstrated abnormalities in prefrontal cortex function. Research has found decreased resting-state prefrontal cortex activity during manic and depressive episodes but increased activity in the anterior cingulate during mania. While generating words in a task, people with bipolar disorder have decreased orbitofrontal cortex activity while manic compared with healthy controls. Other research has found increased prefrontal cortex activity during a verbal fluency test, decreased dorsolateral prefrontal cortex activity when viewing fearful faces as compared with healthy controls, and decreased ventral prefrontal cortex activity during cognitive control tasks.

Like structural differences, there have been observed differences in brain function in subcortical and medial brain regions. Research has shown decreased brain activity in a region of the striatum called the caudate in people with bipolar disorder who were experiencing a depressive episode. In contrast, while manic, people with bipolar disorder have increased activity in another area of the striatum called the basal ganglia. This suggests that there are state-dependent (i.e., depressed or manic) patterns of activity in the striatum.

See also Bipolar Disorders: Diagnosis; Family Studies; Genetic Research; Mania; Mixed Episode; Neuroimaging; Twin Studies

David Colin CiceroMallory Klaunig
http://dx.doi.org/10.4135/9781483365817.n191
10.4135/9781483365817.n191

Further Readings

Cousins, D. A., & Grunze, H. (2012). Interpreting magnetic resonance imaging findings in bipolar disorder. CNS Neuroscience & Therapeutics, 18, 201–207. doi:http://dx.doi.org/10.1111/j.1755-5949.2011.00280.x

Kempton, M. J., Geddes, J. R., Ettinger, U., Williams, S. C. R. & Grasby, P. M. (2008). Meta-analysis, database, and meta-regression of 90 structural imaging studies in bipolar disorder. Archives of General Psychiatry, 65, 1017–1032. doi:http://dx.doi.org/10.1001/archpsyc.65.9.1017

Strakowski, S. M., DelBello, M. P., & Adler, C. M. (2005). The functional neuroanatomy of bipolar disorder: A review of neuroimaging findings. Molecular Psychiatry, 10, 105–116.

Walderhaug, E., Varga, M., San Pedro, M., Hu, J., & Neumeister, A. (2011). The role of aminergic systems in the pathophysiology of bipolar disorder. In H. K. Manji & C. A. Zarete (Eds.), Behavioral neurobiology of bipolar disorder and its treatment (pp. 107–126). Berlin, Germany: Springer-Verlag.